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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/164,764	10/01/1998	DAVID SIDRANSKY	01107.76459	7055

7590 02/04/2002

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EXAMINER

SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
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1655

DATE MAILED: 02/04/2002

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/164,764

Applicant(s)

Sidransky

Examiner

Jehanne Souaya

Art Unit

1655



— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Nov 26, 2001
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-32 and 34-45 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 23, 29-32, 35, 36, 39-41, and 43-45 is/are allowed.
- 6) ☒ Claim(s) 24-28, 34, 37, 38, and 42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) ☐ Other: _____

Art Unit: 1655

DETAILED ACTION

1. Currently, claims 23-32, 34-37 and newly added claims 38-45 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. This action is FINAL.

2. The double patenting rejection of claims 24-28 and 37 is maintained on the record. Applicant has indicated that a terminal disclaimer will be filed should claims 24-28 and 37 be found allowable. It is noted that this rejection also applies to newly added claim 42.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. Claims 24-28, 37, and newly added claim 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brugieres et al (Cancer Research, Feb. 1993, vol. 53, pp 452-455) in view of Gonzalez-Zulueta (Cancer Research 1993) Merlo et al., (Cancer Research 1994), and Ah-See et al (Cancer Research, 1994). **It is noted that applicant's amendment including new claim 38 necessitated the inclusion of claim 38 in this rejection.**

Art Unit: 1655

The claims are drawn to a method of detecting cancer of any organ in a specimen of body fluid which drains the organ by detecting an alteration in microsatellite marker length alteration. Brugieres teaches detecting sarcoma in patients by detecting p53 mutations from DNA isolated from total blood. Although Brugieres does not teach detecting cancer by detecting microsatellite length alterations, it was known in the art at the time of the invention that microsatellite length alterations were associated with different forms of cancer. Gonzalez-Zulueta teaches that instabilities include both tri and tetra-nucleotide repeats and both expansion and deletions of repeat units with the microsatellite markers (p. 5620, lines 2-8). Gonzalez-Zulueta teaches detecting such instabilities in patients with bladder and colorectal cancers and suggests that "this kind of instability might be common to all sporadic human cancers (p. 5622, col. 2, lines 22-29). Merlo et al teaches that microsatellite instability (deletions or expansions) were found to be common in small cell lung cancer (p. 2099). Ah-See teaches that LOH was detected in microsatellite markers in patients with Squamous Carcinoma of the Head and Neck (see abstract). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect cancer by detecting microsatellite marker length alterations in a specimen that contains body fluid that drains from an organ. Brugieres teaches detecting sarcoma by detecting DNA mutations from total blood, thus the ordinary artisan would have a reasonable expectation of success that cancer cells could be found in blood and that total blood could be used as a specimen in detecting mutations. From the teachings of Gonzales-Zulueta, Merlo, and Ah-See, the ordinary artisan would have been taught that different types of

Art Unit: 1655

cancer could be detected by detecting microsatellite length alterations and that such instabilities were common in different types of cancer. The ordinary artisan would have been motivated to combine these teachings to arrive at the instantly claimed invention for the purposes of developing a non-invasive (teaching of Brugieres), reliable (teachings that microsatellite length alterations are a reliable indicator of cancer) method of detecting cancer in a patient.

Response to Arguments

The response traverses the rejection. The response traverses that the claimed method is drawn to detecting cancer of an organ by testing a body fluid that drains the organ and that none of the references cited teach this limitation. This argument has been thoroughly reviewed but was not found persuasive because the claim is also drawn to “detecting cancer of an organ in a specimen of a body fluid... wherein the specimen is selected from the group consisting of blood...”. As all organs drain blood and the claims do not specify any organs in particular, the teachings of Brugieres satisfy the claim limitations. The response further traverses that Burgieres teaches testing whole blood samples and thus teaches the identification of mutations that are found in all cells of an individual. This argument has been thoroughly reviewed but was not found persuasive as the claims are not drawn to a specific type of blood sample nor do the claims contain the limitation of testing for only non-germ line mutations. It is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Art Unit: 1655

The response further asserts that none of the teachings of Gonzalez-Zulueta or Merlo or Ah-See teach identification of a cancer by determining microsatellite repeat polymorphisms in a body fluid which drains an organ. This argument has been thoroughly reviewed but was found unpersuasive as the rejection above sets forth that the teachings of Gonzalez-Zulueta and Merlo and Ah-See were cited to show that it was known at the time of the invention that microsatellite repeat polymorphisms were detected in specific types of cancer. Applicants arguments regarding the teachings of Gonzalez-Zulueta and Merlo and Ah-See appear to be directed to the fact that each reference does not teaching every limitation in the claim. However, the references were not cited in a rejection based on 35 USC 102 but on 35 USC 103(a). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For these reasons, and the reasons made of record previously, the rejection is maintained.

4. Claims 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashi et al (Cancer Research, July 1994, vol. 54, pp 3853-3856) in view of Gonzalez-Zulueta (Cancer Research 1993) Merlo et al., (Cancer Research 1994), and Ah-See et al (Cancer Research, 1994).

Art Unit: 1655

Claim 34 is drawn generally to detecting cancer cells in a specimen external to a primary tumor by detecting microsatellite length alterations in a histopathological margin specimen external to a primary tumor.

Hayashi et al teach that discrepancies were found between genetic and histopathological diagnoses in 7 out of 14 cases with respect to presence or absence of cancer cells in lymph nodes, as these patients were histologically diagnosed node negative but genetically diagnosed node positive (see abstract). Hayashi further teaches detecting mutations in 5 of seven total regional lymph nodes where histopathological diagnosis detected no metastasis (see p. 3854, col 2). Therefore, from the teachings of Hayashi, the ordinary artisan would have been taught that cancer cells can be found in regions external to primary tumors and that such cancer cells are not necessarily detectable by traditional histopathological methods. The ordinary artisan would have further been taught the importance of detecting cancer cells in such specimens as Hayashi teaches disease recurs in 20-30% of patients and that therefore, genetic evaluation of lymph nodes for metastasis may become a useful prognosticator.

Although Hayashi does not teach detecting microsatellite length alterations, Gonzalez-Zulueta teaches that instabilities include both tri and tetra-nucleotide repeats and both expansion and deletions of repeat units with the microsatellite markers (p. 5620, lines 2-8). Gonzalez-Zulueta teaches detecting such instabilities in patients with bladder and colorectal cancers and suggests that “this kind of instability might be common to all sporadic human cancers (p. 5622, col. 2, lines 22-29). Merlo et al teaches that microsatellite instability (deletions or expansions)

Art Unit: 1655

were found to be common in small cell lung cancer (p. 2099). Ah-See teaches that LOH was detected in microsatellite markers in patients with Squamous Carcinoma of the Head and Neck (see abstract). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect cancer by detecting microsatellite marker length alterations in a histopathological specimen. Hayashi teaches detecting lymph node metastasis in regional lymph nodes that were histopathologically negative, thus the ordinary artisan would have a reasonable expectation of success that cancer cells could be found in histopathological sections external to a primary tumor and that such could be detected through genetic changes. From the teachings of Gonzales-Zulueta, Merlo, and Ah-See, the ordinary artisan would have been taught that different types of cancer could be detected by detecting microsatellite length alterations and that such instabilities were common in different types of cancer. The ordinary artisan would have been motivated to combine these teachings to arrive at the instantly claimed invention for the purposes of developing a reliable (teachings that microsatellite length alterations are a reliable indicator of cancer) and improved method of detecting metastasis in tissue that would traditionally (histopathologically) be diagnosed as negative (teaching of Hayashi).

Response to Arguments

The response traverses the rejection. The response traverses that the method of claim 34 is not drawn to metastasis. The response further asserts that the specification discloses that the

Art Unit: 1655

histopathological margin specimen is a specimen that surrounds a tumor and cites the teachings of the specification at p. 9, lines 10-18. This argument has been thoroughly reviewed but was found unpersuasive as the specification teaches that a hypermutable nucleic acid sequence associated with a primer tumor can be detected by assaying the surrounding tumor margin. The specification then goes on to define the term "tumor margin". The specification does not teach what is meant by the term "histopathological margin specimen" nor does the specification define or limit the distance encompassed by the phrase "histopathological margin specimen external to a primary tumor" (exact wording in claim) (ie: the distance from the primary tumor encompassed by the term 'external'). It is noted that the features upon which applicant relies (tumor margin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The response further asserts that none of the teachings of Gonzalez-Zulueta or Merlo or Ah-See teach identification of a cancer by determining microsatellite repeat polymorphisms in a histopathological margin specimen of a tumor. This argument has been thoroughly reviewed but was found unpersuasive as the rejection above sets forth that the teachings of Gonzalez-Zulueta and Merlo and Ah-See were cited to show that it was known at the time of the invention that microsatellite repeat polymorphisms were detected in specific types of cancer. Applicants arguments regarding the teachings of Gonzalez-Zulueta and Merlo and Ah-See appear to be directed to the fact that each reference does not teaching every limitation in the claim. However, the references were not cited in a

Art Unit: 1655

rejection based on 35 USC 102 but on 35 USC 103(a). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For these reasons, and the reasons made of record previously, the rejection is maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 1655

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1655

January 30, 2002



W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600